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## REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

### Status of Claims

Claims 24-28 are currently pending, in the application, with claim 24 being the independent claim. Claims 1-23 and 29 were previously canceled. No claims are amended.

## CLAIM REJECTIONS

### 35 U.S.C. § 112 Rejections

The Office Action, at pages 2-16, maintains the rejection of claims 24-28 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner alleges that induction of organized, functional bone formation at a site of bone infirmity by implanting mesenchymal stem cells (MSCs) *without a matrix* is not enabled by the art or the instant specification. Applicants respectfully traverse this ground of rejection.

Contrary to the Office's allegation, Examples 1 and 2 in the specification clearly show successful bone differentiation following transplantation of pluripotent stem cells transfected with BMP-2 in the absence of an exogenous osteoinductive matrix. In particular, Example 1 teaches that transplantation of pluripotent cells transformed with BMP-2 into the abdominal muscle leads to *in vivo* formation of bone collar and cartilage, prominent trabecular bone, cartilage and bone marrow, without the addition of an osteoinductive matrix. Further, Example 2 in the specification teaches that transplantation of pluripotent cells transfected with rhBMP-2 into a segmental defect results in the formation of ectopic bone in the absence of an exogenous osteoinductive matrix.

The lack of requirement for an osteoinductive matrix demonstrates that the transfected cells of the present invention possess an intrinsic ability to generate new bone tissue, a new

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and unexpected property. Accordingly, the specification provides full enablement for bone formation following implantation of transfected cells without a matrix.

Furthermore, contrary to the Examiner's allegation that Applicants' own work (Moutsatsos *et al.* 2001 *Mol. Ther.* 3: 449-61, ("Moutsatsos")) provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation (Office Action at page 5), Moutsatos discloses the following:

Expression of rhBMP-2 in C3H10T1/2 cells can induce differentiation of osteoblastic and chondroblastic cells. These genetically engineered mesenchymal stem cells have an enhanced therapeutic effect in healing bone segmental defect due too a dual mechanism: the paracrine mechanism of rhBMP-2 on host cells and the autocrine mechanism of rhBMP-2 inducing the osteogenic differentiation of the transplanted genetically engineered stem cells themselves.

*Id.* Paragraph bridging pages 449-50.

In addition, Moutsatsos teaches:

Formation of bone by transplanted C9 cells expressing rhBMP-2 was achieved regardless of the carrier being used. C9 cells formed bone when transplanted on a biodegradable collagen carrier and ***even with no carrier at all when injected locally.***

*Id.* at page 460, col. 1 (emphasis added).

Accordingly, Applicants' own work clearly demonstrates the ability of mesenchymal stem cells transfected with BMP-2 to induce bone formation in the absence of any matrix.

Moreover, as previously stated, Examples 3, 8, 9, 11 and 14-15 clearly show that implantation of collagen sponge alone or collagen sponge loaded with cells not expressing BMP-2 causes no bone formation. Contrary to the Examiner's allegation, nowhere do these examples show that the collagen sponge carrier used in the invention becomes osteoinductive.

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Thus, at least for all the reasons stated above, the rejection of claims 24-28 under 35 USC § 112, first paragraph, is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

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### **Conclusion**

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,



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